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Mycobacterium ulcerans disease in the middle belt of Ghana: An eight-year review from six endemic districts

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ABSTRACT

Background: *Mycobacterium ulcerans* (MU) produces mycolactone toxin when infected with a plasmid. Toxin is cytotoxic and immunosuppressive, causing extensive destruction of tissues, leading to large ulcers on exposed parts of the body. Spontaneous healing by secondary intention leads to contractures, subluxation of joints, disuse atrophy, distal lymphedema and other complications. The disease is endemic in some communities within the middle belt of Ghana.

Objective: To document the clinical and epidemiological features of MU disease in the middle belt of Ghana and the outcome of treatment.

Patients and methods: Patients with lesions suspected to MU disease were screened by community workers. Lesions were confirmed by any of the following: direct smear examination, culture, polymerase chain reaction (PCR), or histopathology.

Patients were treated with rifampicin (10 mg/kg orally) and streptomycin (15 mg/kg IM) combination for eight weeks. Patients selected for surgical treatment included cases where medical treatment had failed, cases where medical treatment is contraindicated, cases presenting late with complications and recurrent cases.

Results: 258 patients were seen in the Ahafo Ano, Amansie Central, Amansie West, Asunafo, Asutifi, and Upper Denkyira districts of Ghana between 2005 and 2012. Their ages ranged from 1 year 3 months to 98 years, with a mean age of 29.8 (SD 20.4).

The clinical forms of MU disease seen were: papule (0.5%), nodule (1.5%), chronic osteomyelitis (1.5%), contracture (1.5%), edematous lesion (3%), and ulcer (92%). Uncommon complications include subluxation of knee joint, salivary gland fistula and Marjolin's ulcer.

The lesions were distributed as follows: head and neck (6.8%), upper limb (20.3%), trunk (1.7%), and lower limb (71.2%).

Conclusion: MU disease in the middle belt of Ghana can be controlled by early case detection and adequate curative treatment.

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Introduction

Mycobacterium ulcerans (Buruli ulcer) disease occurs most frequently in tropical and subtropical areas that are marshy or near lakes and rivers. The disease has been reported worldwide from Australia, Japan, Papua New Guinea and China. Benin, Cote d'Ivoire and Ghana are the most endemic countries in Africa [1]. Cases in Ghana were identified in all 10 regions, and in 90 (81.8%) of the then-110 districts in a national case search in 1999 [2]. Some of the districts known to be endemic in Ghana include Ahafo Ano, Amansie Central, Amansie West, Asunafo, Asutifi, and Upper Denkyira [3,4]. These communities are found in Ashanti, Brong Ahafo, and Central regions. They form part of the middle belt of Ghana, which has rain forest as the vegetative cover. The middle belt is drained by several rivers, some of which enter the sea directly or are tributaries of rivers entering the sea. In addition, there is an inland lake in Ashanti. Six communities in the drainage area of Tano (Ahafo Ano, Asunafo, and Asutifi) and Offin (Amansie Central, Amansie West, and Upper Denkyira) rivers were the setting for the current study.

The etiological agent of Buruli ulcer (BU) disease is *M. ulcerans* (MU), an acid fast bacillus, which can be cultured on Lowenstein Jensen medium at a temperature of 30 °C–33 °C [5]. Analysis of its complete genome sequence has revealed the presence of a set of three large genes which is responsible for the production of mycolactone [1], a toxin which has cytotoxic and immunosuppressive properties [6]. This toxin is produced when the MU is infected with a transmissible plasmid [7]. This toxin is mainly responsible for the pathology of MU disease [8]. Infection with MU often leads to extensive destruction of tissue with the formation of large ulcers, especially on the limbs and other exposed parts of the body, such as the head and neck [9]. Spontaneous healing of the ulcers may occur, but may lead to considerable deformity, such as contractures, subluxation of joints, disuse atrophy, and distal lymphedema [5]. The mode of transmission of MU disease is not known, though MU has been found in biofilms, soil, aquatic insects, water bugs, fish and wildlife [10]. The disease is classified into non-ulcerative and ulcerative forms [11]. The non-ulcerative forms include the papule (Fig. 1), nodule (Fig. 2), plaque and edematous forms. The ulcer typically has undermined edges, indurated peripherally, and may have white cotton wool-like slough (Fig. 3). The active MU lesion is usually painless unless there is a secondary bacterial infection [5].

Initially surgical excision was the standard treatment, and when performed at an early stage of the disease, was curative. Unfortunately, most patients present late with advanced disease (Fig. 4), requiring wide surgical excision and skin grafting, or occasional limb amputations [11]. The World Health Organization (WHO) in March 2003 recommended the daily administration of rifampicin and an aminoglycoside, usually streptomycin, for eight weeks as the first-line treatment for all forms of active MU disease. Surgery was recommended to remove necrotic tissue, cover skin defects and correct deformities. Interventions were to be instituted to prevent or minimize disabilities [12].



Fig. 1 – A papule on the leg of a 13-year-old girl in a BU endemic community.



Fig. 2 – A nodule on the upper arm of a 9-year-old boy in a BU-endemic community.



Fig. 3 – Typical Buruli ulcers on the cervical and sub-mental regions of an 8-year-old girl.



Fig. 4 – Buruli ulcer on the lower limb of a 27-year-old farmer requiring wide excision and skin grafting.

The current study was undertaken to document the clinical and epidemiological features of MU disease in the six endemic districts, within the period from January 2005 to December 2012, and to assess the outcome of medical and surgical treatment offered. This knowledge could help in determining the disease pattern in the middle belt of Ghana, and to determine the optimal treatment modality for the disease in the Ghanaian situation based on WHO recommendations.

Patients and methods

Community workers specially trained under the National Buruli Ulcer Control Program identify patients with all forms of MU disease in the endemic communities. These are referred to the district hospitals where they are examined clinically by the doctor and the diagnosis confirmed by direct smear and microscopy of tissues from lesions, culture on Lowenstein Jensen medium, histopathology of tissue obtained at surgery or polymerase chain reaction (PCR). The latter two tests could only be done at Komfo Anokye Teaching Hospital or the Kumasi Centre for Collaborative Research (KCCR) into Tropical Medicine.

Confirmed active cases were treated with intramuscular streptomycin (15 mg/kg) and oral rifampicin (10 mg/kg) in combination for eight weeks. Patients selected for surgery include those with unhealed lesions after completion of antibiotic treatment, those in whom medical treatment had failed, those in whom medical treatment is contraindicated and those presenting with complications of MU disease.

Patients were included in the study if they were treated for MU disease between the period from January 2005 to December 2012; their diagnoses of MU disease have been confirmed by any of the above 4 tests; have completed 8 weeks of streptomycin and rifampicin combination; and/or undergone surgery for MU disease or its complications.

Ethical approval for the study was obtained from the Committee on Human Research Publication and Ethics (CHRPE) of Kwame Nkrumah University of Science and Technology in Kumasi. All the patients or their parents, in

the case of children, consented to participate in the study. They also consented to the use of their clinical pictures for teaching purposes and for the dissemination of knowledge of MU disease.

Results

A total of 518 patients were seen at Ahafo Ano, Amansie Central, Amansie West, Asunafo, Asutifi, and Upper Denkyira districts of Ghana from 2005 to 2012. Their ages ranged from 1 year 3 months to 98 years; the mean age was 29.8 (SD = 20.4).

The distribution of the MU lesions on the body were as follows: head and neck (6.8%), upper limbs (20.3%), trunk (1.7%) and lower limbs (71.2%). The clinical forms of the disease were as follows: papule (0.5%), nodule (1.5%), edematous lesion (3%), ulcer (92%), osteomyelitis (1.5%) and contracture (1.5%). There were three uncommon complications: subluxation of knee joint (one case), salivary gland fistula (one case), and Marjolin's ulcer (one case).

260 patients were treated solely with streptomycin and rifampicin, and their lesions healed completely; they did not require any surgery (Figs. 5a–d). 258 patients either had antibiotics and surgery, or had surgery alone. The types of surgical procedures performed are shown in Table 1.

Discussion

Even though the mode of transmission of the disease is not precisely known, the distribution of the lesions in this study, with a higher concentration on the limbs, especially the lower limbs (71.2%), and the head and neck region of children (6.8%) (Fig. 3), supports the findings of other workers [2,9,10,16] that MU is an environmental pathogen, transmitted probably close to the ground, in an aquatic environment, such as prevails in the middle belt of Ghana.

Most of the MU lesions (92%) were ulcers, requiring excision and skin grafting (71%) after antibiotic treatment. The earlier clinical forms of the disease, such as the papule (0.5%), the nodule (1.5%) and the edematous lesion (3%), which can be cured either by surgery or by antibiotics, appear to be fewer in this series. These lesions can easily be mistaken for reactions to insect bites, allergic reactions, or minor injuries common in the environment. Pure MU lesions are generally painless, unless there is secondary bacterial infection [5]; hence, such cases are likely to be ignored by the patients. Inexperienced field workers may also not consider such lesions to be due to MU disease, thus explaining the rarity of the early stages.

The efficacy of streptomycin/rifampicin combination in the treatment of MU disease has been demonstrated in several series [13,14] and in Fig. 5. When instituted early in active disease, the antibiotic combination may limit the extent of, or obviate the need for surgery. The combination of surgery and antibiotics provides optimal results in the management of MU disease [15]. However, for patients presenting with contractures, surgery remains the main option since antibiotics have no role in a situation where there are no organisms.

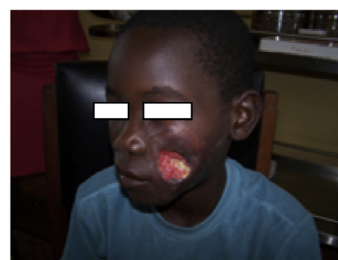
Mycobacterium ulcerans disease of the face

Before antibiotic treatment

two weeks after rifampicin & streptomycin treatment



a



b

Mycobacterium Ulcerans disease of the face

Four weeks after antibiotic treatment

Healed wound after 8 weeks of antibiotic treatment



c



d

Fig. 5 – Effect of streptomycin/rifampicin therapy for MU disease of the face.

Table 1 – Surgical procedures performed for 258 patients with MU disease.

Surgical procedure	Percentage (%)
Wound excision and skin grafting	71
Release of contracture	11
Wound debridement	8
Skin grafting	5
Sequestrectomy	2
Others	3

Conclusion

The middle belt of Ghana provides an ideal environment for *M. ulcerans* disease to thrive. Eradication of the disease would involve breaking the cycle of transmission, which is currently not precisely known. Adequate control can, however, be achieved by detecting the disease at an early stage where curative treatment can be offered.

Conflict of interest

We have no conflict of interest to declare.

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